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Review Article

Gallbladder metastasis of clear cell renal cell carcinoma: A case report and review of literature

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ABSTRACT

Renal cell carcinoma (RCC) is the 3rd most common malignancy in adults including both male and female. Clear cell RCC is the most common type of RCC, and it accounts for 70% of all cases. RCC is prone to get metastasize but its metastasis to gallbladder is quite rare. Various radiological modalities like ultrasound and CT scan can easily pick up gallbladder metastasis at an early stage. Along with our case report we will be review various articles published in literature and will be discussing various parameters of this rare occurrence also try to understand its pathogenesis. Early detection and appropriate treatment can improve the prognosis.

1. Introduction

Renal cell carcinoma (RCC) is the 3rd most common malignancy in adults including both male and female.[1] Clear cell RCC is the most common type of RCC, and it accounts for 70% of all cases.[2] RCC is prone to get metastasize but its metastasis to gallbladder is quite rare. Most common sites to metastasize are lung (75%), bones (20%), liver (18%) and skin (8%), and brain (8%).[3] For gallbladder the most common tumor to get metastasize are gastric cancer, RCC, hepatocellular carcinoma, colon.[4] Overall survival of patients with metastatic RCC who have undergone metastatectomy is better.[5]

Here we are reporting a case of patient of RCC with gallbladder metastasis which is a rare site for metastasis of RCC. Till to date only a handful cases of RCC with gallbladder metastasis have been published in literature. There is no well characterization of pathophysiology behind such kind of metastasis, its clinical and prognostic significance and its impact on overall survival. In this article along with our case report we will be review various articles published in literature and will be discussing various parameters of this rare occurrence also try to understand its pathogenesis.

2. Materials and Methods

A 68 years old gentle man diagnosed and treated outside in March 2020, where he presented with complains of generalized weakness, hematuria and dysuria. On further evaluation he was diagnosed with right renal neoplastic lesion with pyelonephrosis with sepsis. CECT abdomen revealed enlarged right kidney with heterogenous enhancement and perinephric fat stranding with few lobulated lobulated cortical lesions with internal hypodensity seen in the upper pole of right kidney, fluid collection with blood clots in right pelvicalyceal system, entire right ureter and also in urinary bladder lumen; likely pyelonephritis or renal neoplasm. Few ill-defined hypodense areas also seen in caudate lobe, segment V

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and VI of liver. Patchy hypodense areas in IVC, partially occluding the lumen thrombosis. Prominent mesenteric and perinephric veins were also seen. MRI OD abdomen showed diffusely swollen right kidney and large multilobulated mass in upper pole, intraluminal thrombosis in right renal vein and intra-hepatic part of IVC. For this Right radical nephrectomy was done, on gross examination 17 x 12 cm tumour was seen involving upper, middle and lower lobes of kidney with extension to renal sinus and renal vein. There was no extrarenal extension. On microscopy diagnosis of renal cell carcinoma (RCC) was made. On IHC the tumour cells were positive for CD10, RCC antigen, Vimentin and PAX5; were negative for CK7 suggestive of Clear cell RCC. After 3 months biopsy from liver lesion was done which revealed infiltration by poorly differentiated tumour. After 4 months he presented to our institute with complains of pain at the surgical site and hematemesis. FDG-PET showed avid and non-avid lesions in liver, bilateral lung and abdominal lymph nodes. Patient for started on Sunitinib. With sunitinib he developed oral ulcers so the drug was stopped for one week. And then started with half dose. After 4 months ultrasonography showed gallbladder wall thickening with echogenic mass at the body and fundus of gallbladder (Figure 1) and PET-CT showed focal tracer uptake in the abdomen on right side corresponding to lesion in body and fundus region of gallbladder (Figure 2) there was distension of gallbladder with wall thickening. FNAC from gallbladder showed poorly differentiated carcinoma. For which Biopsy was done which confirmed features of metastatic RCC.

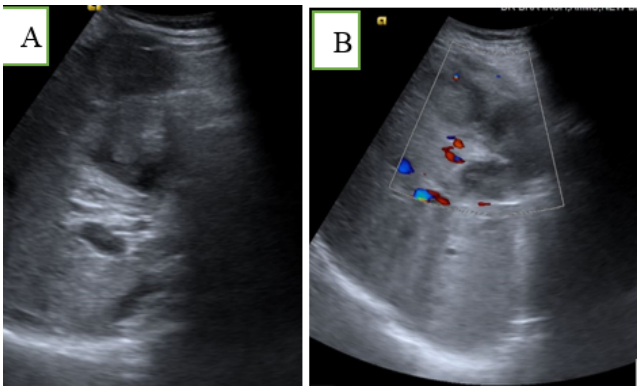

Figure 1: Gall bladder mass in a patient of RCC. Ultrasound image showing gallbladder wall thickening with echogenic mass (white arrow) occupying the lumen of fundus and body of GB (**A**) and show no significant internal vascularity (**B**)

Along with our case we have collected 41 cases of metastasis of RCC into gallbladder published in PubMed index (Table 1). The data was collected from year 1991 to 2021. Almost all prior reports of RCC metastasis to gallbladder have reviewed many parameters including demography, histology, timing of presentation, clinical presentation, concomitant metastasis of two other organs

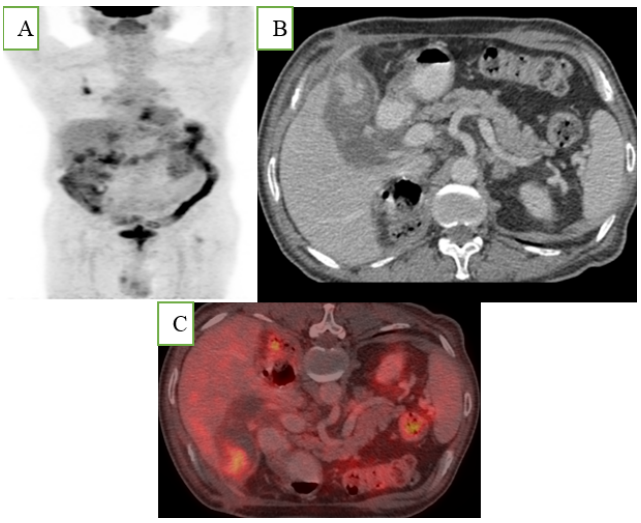

Figure 2: A: Maximum intensity projection image of FDG PET-CT showing focal tracer uptake in the abdomen on right side corresponding to lesion in body and fundus region of gallbladder (**B**) on axial CT section showing increased tracer uptake in the fused PET-CT image (**C**).

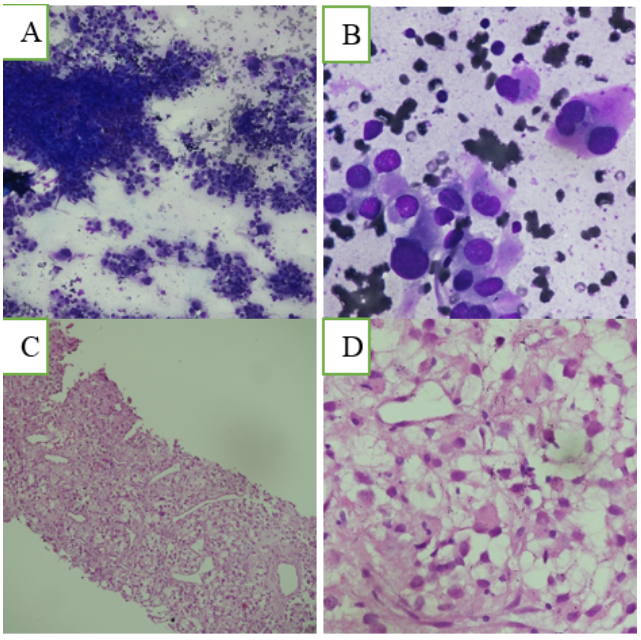

Figure 3: A,B: FNAC smears were cellular showing pleomorphic population of tumor cells with abundant cytoplasm, focally forming tumor giant cells. **C,D:** Histologically tumor cells are fibro-collagenous tissue infiltrated by large polygonal cells with abundant eosinophilic cytoplasm.

Table 1: Cases of metastasis of RCC into gallbladder published in PubMed index

S.No.	Study	Year	syn/meta	References
1	Satoh et. al.	1991	sync	6
2	Fullarton et. al.	1991	meta	7
3	Golbey et. al.	1991	meta	8
4	Nagler et. al.	1994	meta	9
5	Pagano et. al.	1995	syn	10
6	King et. al.	1995	syn	11
7	Finkelstein et al.	1996	meta	12
8	Lombardo et. al.	1996	meta	13
9	Sparwasser et. al.	1997	meta	14
10	Celebi et. al.	1998	syn	15
11	Kechrid et al.	2000	meta	16
12	Aoki et. al.	2002	meta	17
13	Aoki et. al.	2002	meta	17
14	Limani et. al.	2003	meta	18
15	Park et al.	2003	meta	19
16	Ishizawa et al.	2006	meta	20
17	Hellenthal et. al.	2006	syn	21
18	Nojima et al	2008	syn	22
19	Sand et al	2009	meta	23
20	Patel et al	2009	meta	24
21	Kawahara et al.	2010	syn	25
22	Shoji et al.	2010	meta	26
23	Fang et al.	2010	meta	27
24	Fang et al.	2010	meta	27
25	Fang et al.	2010	meta	27
26	Fang et al.	2010	meta	27
27	Chung et. al	2010	meta	28
28	Chung et. al	2010	syn	28
29	Chung et. al	2010	syn	28
30	Chung et. al	2010	syn	28
31	Decoene et al.	2011	meta	29
32	Jain and Chopra	2013	meta	30
33	Ueda et al.	2014	meta	31
34	Saito et. al.	2018	meta	32
35	K Takagi et. al.	2019	syn	33
36	I white et. al.	2019	meta	34
37	T Oba et. al.	2020	meta	35
38	I Maggio et. al	2020	meta	36
39	SH Cho et. al.	2021	syn	37
40	DP Pierce et. al.	2021	syn	38
41	E Rahul el.al. (present study)	2021	meta	

and their follow up. All those articles were excluded which were not published in English. Survival analysis was concluded using log-rank Kaplan-Meier analysis.

3. Results

We have collected total 40 cases from reviewed articles and 1 (total 41 cases) case from our institute. There was marked prominence of male as female incidence was seen only in 13 cases. The median age of presentation was 62.5 years. Of the collected patients, most of them had histology of Clear cell RCC (37 cases). In 3 of the cases, no histomorphological type was specified and 1 had papillary RCC histology. 28 were having metachronous involvement with median duration of 28 months (0.6 year to 27 years).

11 Patients presented with clinical symptoms of acute cholecystitis (epigastric pain, heart burn, nausea, vomiting etc.) while rest of the patients were asymptomatic and were diagnosed incidentally on regular follow up. Most common modality used was CT scan (32 patients). Other modalities used were ultrasonography, MRI and X-ray; of which ultrasonography was second most common modality used in

Table 2: Clinical and morphological characteristics of 40 cases from reviewed articles and 1 (total 41 cases) case from our institute

Parameters	Characteristics	Percentage
Age	62.5 (39-84 years)	
Sex		
Male	28	68.3
Female	13	31.7
Duration after RCC diagnosis		
Synchronous	10	24.4
Metachronous	31	75.6
Side of RCC		
Right	24	58.5
Left	17	41.5
bilateral	1	2.5
Histological subtype		
Clear cell RCC	37	90.2
Papillary RCC	1	2.5
No histology specified	3	7.3

Table 3: Diagnostic modalities and management done on 40 cases from reviewed articles and 1 (total 41 cases) case from our institute

Parameters	Characteristics	Percentage
Size of GB mass	3 cm (0.5 – 7.5 cm)	
Symptoms		
Symptomatic	11	27
Asymptomatic	30	73
Investigation used		
CT	32	78
USG	26	63
MRI	6	15
FDG-PET	3	7.3
X-Ray	2	4.9
Type of lesion on radiology		
Mass	36	88
Wall thickening	3	7.3
Not specified	2	4.9
Surgical procedure		
Simple cholecystectomy	27	66
Extended cholecystectomy	5	12.2
Laparoscopic cholecystectomy	9	22

25 patients. On CT scan showed the mass with high density on arterial enhanced phase image. On ultrasound, they were echo bright on the surface, indicating submucosal tumor.[39] Most of the patients presented with gallbladder mass. But 3 patients presented with indistinct wall thickening with no evident mass lesion. The mass varied from 0.5cm to 7.5cm. In our patient, ultrasonography showed echogenic lesion involving the lumen and causing wall thickening with echogenic mass measuring ~2 cm in the fundus and body of gallbladder; On CT gallbladder appeared distended with evidence of metabolic active lesion in body and fundus of gallbladder. Of all the patients, 20 patients had only gallbladder involvement and 21 patients had synchronous or metachronous metastasis to other organs also. Most common site other than gallbladder was lung (11 patients). Other less common sites were contralateral kidney, adrenal pancreas, skeletal muscles, brain etc. 27 patients underwent simple cholecystectomy. 5 underwent extended cholecystectomy. 9 patients underwent laparoscopic cholecystectomy, including ours.

Median follow up after cholecystectomy was 1.4 years (range 0.08 to 11 years). 19 cases were doing well with combined therapy when followed-up. 8 patients died and for 13 cases, no follow up data was present.

As follow-up data was not present for all of the cases. Of all 15 patients with metastasis only to gallbladder were followed for median time of 27 months after cholecystectomy. Two of the patients with only gallbladder metastasis died during the follow because of metastasis to other organs. Whereas, 13 patients with metastasis only to other organs along with gallbladder were followed for median time of 30 months after cholecystectomy. Of all the patients with multiple organ involvement 6 patients died, 4 because of multiple organ metastasis, 1 because of MI (myocardial infarction) and the cause of death was not known for 1 patient. Kaplan-Meier analysis was conducted to compare difference in the survival between the cases with metastasis only to the gallbladder and those with metastasis to other organs. It was contributed according to following Figure 4., the survival was better in patients with only gallbladder involvement as compared to patients with multiple organ involvement.

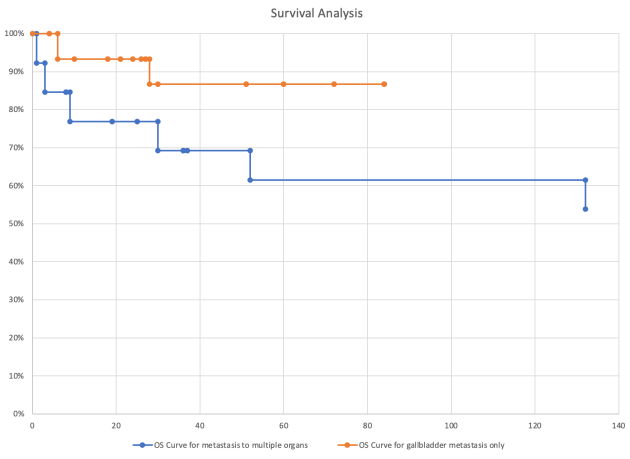

Figure 4: Kaplan-Meier graph for overall survival

Table 4: Other organs involved and follow up details of 40 cases from reviewed articles and 1 (total 41 cases) case from our institute

Parameters	Characteristics	Percentage
Synchronous		
To GB only	8	19.5
To multiple organs	6	14.6
Metachronous		
To GB only	20	48.8
To multiple organs	8	19.5
Other organs involved		
Lung	11	27
Contralateral kidney	11	27
Bone	6	14.6
Pancreas	5	12.2
Adrenal	4	9.8
Muscle	2	4.8
Brain	2	4.8
Peripheral Nerves	2	4.8
Ovary	1	2.5
Thyroid	1	2.5
Spine	1	2.5
scalp	1	2.5
Follow-up duration	**(1month- 11 years)**	
Events		
No evidence of disease	18	44
Alive with metastasis	2	4.8
Death from metastasis	6	14.6
Non-cancerous death	2	4.8
No follow-up	13	32

4. Discussion

After extensive search we have reviewed the literature and have concluded that only a handful number of case reports are available. Although, the number of cases we have retrieved are very less to definitely address the characteristics of patients RCC with gallbladder metastasis and reach to a definite conclusion, still we have highlighted few salient points about the demographic features, pathophysiology and prognostic factors associated with this rare pathology.

The differentiation of primary vs. secondary gallbladder cancer is very challenging. Primary gallbladder cancer is mostly associated with gall stones. However, acalculous gallbladder is more consistent with metastasis than a primary tumour[40]. Histologically, primary tumours of the gallbladder are most commonly adenocarcinomas; however, immunohistochemical staining is necessary to accurately differentiate between primary and metastatic gallbladder tumours[17]. Treatment options for metastatic tumours within the gallbladder are not clear. However, whether the gallbladder tumour is primary or secondary, cholecystectomy is necessary in patients with symptomatic gallbladder to avoid symptoms or complications.

We have found that this association is more common in males as compared to females. Instead, primary adenocarcinoma of gallbladder, which is more common in females.[41] This can be because of known fact that RCC itself is more common in males as compared to females, so its metastasis will also be more common in male.[1]

We have found out that the most common histological subtype of RCC associated with gallbladder metastasis is Clear cell RCC (seen in 90% of cases). This can be because of Clear cell RCC being the most common subtype of RCC.[1] This coincidence can be because of small sample size of our cohort. Although, in our review we have got only one case which was associated with papillary RCC.

We have seen that metastasis of RCC to gallbladder is through hematogenous spread and not through direct invasion. For most of the cases reviewed, the lesion on the gallbladder was with a mass lesion protruding into the lumen of the gallbladder or as a wall thickening. However, no breach or erosion on the serosal surface was seen. The median time for occurrence of metastasis was 13.5 years. These evidences favor that metastasis to gallbladder is not through direct invasion. Instead it is through either through hematogenous or lymphatic spread. Hematogenous being most common type of mode of metastasis in clear cell RCC.[42,43]

The incidence of occurrence of concomitant metastasis to other organs of the body is same in these cases as seen in cases with RCC without gallbladder involvement. In our case, the most common concomitant metastasis was found in lungs and contralateral kidney, each seen in 27% of the cases.[3,28] The third most common site for metastasis was bone followed by pancreas (15% and 12%, respectively).

As seen in study done by Kavolius JP et al, the 5-year survival rate following metastatectomy of solitary metastasis from RCC ranges from 35-50%.[5] However, in our study cases with solitary gallbladder metastasis were not followed up for relatively less duration after cholecystectomy to definitely predict the overall survival rate.

The treatment of choice for gallbladder malignancy either primary or secondary is cholecystectomy. In our cohort, all of the patients underwent cholecystectomy with or without chemo/immunotherapy. The impact of cholecystectomy with adjuvant chemotherapy on survival of the patient cannot be concluded because of small sample size.

There are so many demerits in the current study because of limited sample size. There was no standard diagnostic and management protocols used in deferent case reports. Which may not reflect the correct picture of the current disease. To our knowledge we have tried to do extensive review of the case reports/ studies of RCC with gallbladder metastasis. Our efforts may help the future clinicians to

better understand and do researches to further improve the survival of patient of RCC with gallbladder metastasis.

5. Conclusion

Gallbladder metastasis from RCC is a rare event, but its diagnosis at an early stage can improve the patient's survival. Various radiological modalities like ultrasound and CT scan can easily pick up gallbladder metastasis at an early stage. Early detection and appropriate treatment can improve the prognosis.

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7. Conflict of Interest

None.

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